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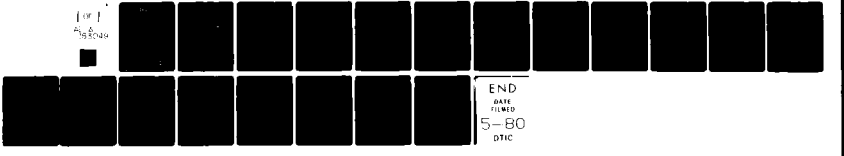

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REPORT NO. 1

# LASSA FEVER IMMUNE PLASMA

Annual Summary Report

John D. Frame, M.D.
Division of Tropical Medicine
School of Public Health, College
of Physicians and Surgeons,
Columbia University

August, 1979

Supported by

U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
Fort Detrick, Frederick, Maryland 21701

Contract No. DAMD-17-79-C-9024

Trustees of Columbia University
in the City of New York
New York, N.Y. 10032



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Lassa fever immune plasma is being obtained in Liberia, West Africa for the U.S. Army Medical Institute of Infectious Diseases by Columbia University associated with the Liberian Institute for Biomedical Research (LIBR). Additionally, epidemiological investigations of Lassa virus infections are proceeding in that country. Indirect fluorescent antibody testing is being carried out at the LIBR by a Liberian team trained by personnel from VILAB II of the New York Blood Center. Field epidemiological investigations are being conducted by the —

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# 19. Fluorescent antibodies

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~Liberian team and the Principal Investigator.

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Summary:

A program to obtain Lassa fever immune plasma for the use of the U.S. Army Medical Research Institute of Infectious Diseases has been inaugurated in Liberia. Initial steps have been the negotiation of a subcontract with the Liberian Institute for Biomedical Research with whom agreement covering the conduct of the research had been made previously. Negotiations have also been made with the New York Blood Center for the instruction and training of Liberian workers to conduct serological testing in Liberia. Sera have been collected in two hospitals in the region of Liberia highly endemic for Lassa fever to determine the incidence of Lassa virus infections in them. When the subcontract with the LIBR has been completed, field investigations will be conducted to determine the incidence of Lassa virus infections in various populations in Liberia, and to discover potential donors for Lassa fever immune plasma.

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## Statement of the Problem:

Investigations of Lassa fever, a recently discovered viral disease of West Africa are somewhat limited by the risk the disease poses to the investigator. The availability of immune plasma from convalescents from this infection would provide needed protection, as well as material to be used in the investigations proper.

## Background:

Since its discovery in Nigeria in 1969, Lassa fever has been identified in a number of hospital outbreaks, with case fatality rates in the range of 35-40% (1,2,3,4). Subsequently, serological evidence of viral activity has been found to be widespread throughout West Africa (5), though some investigations have suggested that the disease is not as uniformly severe as the experience of hospital outbreaks indicated (6,7). At present, it is unclear what factors in the agent or host may influence the severity of the clinical infection.

It would appear that so widespread and potentially so lethal a disease would deserve intensive investigations of the nature and epidemiology of the virus, and development of a vaccine for the protection of populations at risk. However, investigations have been limited to date in part because of meager financial resources for research, and more significantly, because of the risk to the investigator. Presumably in response to this situation, and following preliminary conversations with Col. Gerald Eddy of the U. S. Army Medical Research Institute of Infectious Diseases, the USAMRIID wrote this institution in 1977 indicating its interest in the development of a vaccine protective against Lassa virus infections and inviting a proposal for the procurement of Lassa fever immune plasma and Congo virus immune plasma, and the development of data regarding the prevalence and disease attack rate of Lassa fever in the area where plasma was to be obtained.

## Approach to the Problem:

A pilot study funded by the Rockefeller Foundation has been conducted in Liberia since 1976 (7). Previous investigations had indicated that the region where Sierra Leone, Guinea and Liberia join was highly endemic for Lassa virus infections (3,4,8), and the political situation in Liberia appeared to be such that the investigations in Liberia did in fact demonstrate that Lassa virus infections were highly prevalent in Lofa County in its West; Lassa virus antibody prevalences among indigenous hospital personnel in the area were from 10 to 23% (7). Prevalences in other parts of Liberia, in the range of 4 to 7%, were not negligible, but Lofa County was selected as the main area of investigation.

Biomedical research in Liberia is conducted under the auspices of the Liberian Institute for Biomedical Research (LIBR), Dr. Emmet A. Dennis, Director, and this institution was appointed by the Ministry of Health of the Republic of Liberia as the organization with which the Lassa Fever Immune Plasma program should be affiliated. An agreement between Columbia and the LIBR was negotiated with some delays because of questions related to the collection of plasma, and doubts about the adequacy of the proposed investigations to meet the needs of Liberia. The final agreement included:

1. Recruiting and employment within Liberia of a Field Investigator with a Bachelor's degree in bioscience or nursing, and a Field Assistant with a background as laboratory technician to be trained and to assist in the filed aspects of the investigation.

2. Repeated serological surveys of selected villages to determine the incidence and prevalence of Lassa virus infections in them, and to discover persons with antibody titers adequate to qualify them as potential donors.

3. Repeated serological surveys of hospital personnel in the endemic area, to determine the incidence of Lassa virus infections in them, and to discover potential plasma donors.

4. Monitoring of patients hospitalized with fever to discover cases of Lassa fever who upon recovery could be asked to become plasma donors.

5. Initial surveys of staffs of Liberian hospitals not already discovered to determine the prevalence of Lassa virus antibodies in other parts of the country.

6. Development within Liberia of the capacity to conduct serological testing for Lassa virus antibodies.

Parts of our plan still to be implemented include the conclusion of a sub-contract with the LIBR formalizing the arrangements already agreed upon. Thereafter the Liberian staff will be employed and trained in the basic elements of epidemilogy and specific procedures to be followed in the field, and be instructed in serological techniques. Training in serological techniques and supervision of the procedures during the first part of the project will be done by professional staff of the VILAB II, New York Blood Center.

A protocol has been prepared to guide the handling, identification, storage and disposition of specimens which will be tested at the LIBR, and is attached as Appendix A of this report.

The Principal Investigator will proceed to the field accompanied by the Liberian team, to villages selected by arrangement with the Ministry of Health and Social Services, and after consultation with the local hospitals. There, after enlisting the cooperation of village leadership and obtaining appropriate consent, blood will be obtained from villagers and tested for viral antibodies. Villagers found to be positive in an adequate titer will be approached and requested to donate plasma, again after the procedures and risks have been explained to them and after consent has been obtained.

At the same time, procedures will be set up in the nearby Lofa County hospitals for the regular testing of patients with fever; those found positive for Lassa virus antibodies will be asked, during their convalescence, to consent to donate blood by plasma-pheresis.

An informational document suitable to instruction of Liberian ministries and other governmental units, and for all organizations which may participate in investigations in Liberia is attached as Appendix B of this report. It describes the village surveys mentioned above, and the other investigations agreed upon by Columbia and the LIBR.

Results:

The major effort in the six months since the beginning of the project has been to complete a subcontract with the Liberian Institute for Biomedical Research. The original subcontract submitted by Columbia was unsatisfactory to that institution, in part because of misunderstandings of the nature of a subcontract and of the single year's funding, and the lack of a component enabling the development of the capability to conduct testing for Lassa virus antibodies in Liberia. The acceptance by the USAMR&D Command of a supplementary proposal for the testing for Lassa virus antibodies in Liberia and the re-writing of the subcontract to reaffirm Columbia's commitment to all aspects of the previously negotiated collaborative arrangements. The LIBR has accepted the terms of the revised subcontract; at present only formal signature remains before its provisions are put into effect.

The preparation of the proposal to the USAMR&D Command for the conduct of serological tests in Liberia, requested by the Command during discussions of the original proposal, required negotiations with the New York Blood Center; its VILAB II, situated at the LIBR in Liberia, offers facilities and personnel for the training of Liberians in

serological technique and supervision of the testing. Mutually satisfactory arrangements have been worked out; their implementation awaits the acceptance by the Liberians of their subcontract.

In the meantime, sera have been collected from personnel of the two hospitals in Lofa County, Liberia, where the prevalence of Lassa virus antibodies was found to be highest in previous investigations. Comparison with the results of tests in 1976 in one, and in 1976 and 1977 in the other will permit initial estimates of the incidence of Lassa virus infections in them. The sera will be tested in the autumn, when they are returned to the United States; aliquots of the specimens will form the first material to be tested in Liberia as well.

Up to the present no major purchases of equipment and supplies have been made; it has seemed prudent to postpone this until the subcontract has been made. However, vendors have been selected, and the purchases will be completed as soon as the subcontract has been signed.

## Conclusions

The procurement of Lassa virus immune plasma and the investigation of epidemiologic aspects of Lassa fever requires close cooperation and mutual understanding between the back county and the research institution. These desirable objectives have apparently been attained in the negotiations between Columbia and the LIBR. Together with the authorization for serological testing for Lassa virus antibodies in Liberia a strong basis for continued work in Liberia has been built.

The project should now be able to continue toward its objectives. By the end of its first year most of the original goals for the year will have been reached. Continuation of the program through its second year will enable the procurement of Lassa fever immune plasma and the delineation of factors related to the distribution, incidence and severity of Lassa fever in Liberia.

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# APPENDIX A

Protocol: Handling, identification, storage and disposition of specimens for serological testing at the LIBR

## 1. General measures

1.1 All specimens obtained by venipuncture will be labeled with a code number identical to that used in the roster maintained at the time the specimen is maintained.

1.2 The roster will indicate in the "Remarks" section any history of fever, and the date of its onset.

1.3 The blood tubes will be stored in a cool place until clot retraction has taken place; at such time serum will be transferred to vial or other container supplied for its storing and transportation.

1.4 The vial will then be labeled at once with the code number of the specimen.

1.5 The vial will be stored in a freezer or designated part of a freezing unit of a refrigerator until time for transport to the LIBR.

## 2. Acute stage specimens

Sera obtained from patients within 4 weeks of the onset of a fever, whether the patient be in a hospital, clinic or his home, will be considered potentially viremic, unless the course of the patient's subsequent illness indicates that he did not have a viral illness. Such specimens will be handled as follows:

2.1 The label of the blood tube will bear a red mark or sign of the potential hazard.

2.2 Separation of serum will be done only by specially designated personnel.

2.3 The vial to which the specimen has been transferred will also bear a red marker or warning label; it shall be placed in the freezer only in special plastic containers with lids designated for this purpose and also bearing warning labels.

2.4 In the freezer and during subsequent transportation the containers for the vials will themselves be placed within plastic bags or other plastic containers capable of being closed.

2.5 These packages will not be opened at the Lassa virus serological laboratory of the LIBR but will be stored until they are shipped by designated means to a containment laboratory equipped for further virological investigation.

3. Survey and convalescent specimens

Specimens obtained from patients with no history of recent fever, or when the date of onset of fever was more than four weeks prior to date of serum collection will be considered virus free, and will be treated as follows:

3.1 Vials will be stored in freezers in containers other than those used for acute stage specimens.

3.2 When the vials are transported to the Lassa fever serological laboratory they will be accompanied by copies of the rosters prepared at the time the blood was obtained.

3.3 Whenever the specimens are to be tested, they will be checked against the roster of specimens to determine that in fact no specimen was obtained within four weeks of the onset of a fever. This procedure will be carried out by the Principal Investigator, the Field Investigator, the Technical Consultant or other person who may subsequently be specifically chosen for this duty.

3.4 After this person has satisfied himself that the specimen is not an acute stage specimen, as described above, he shall release it for appropriate serological testing.

# APPENDIX B

## Lassa Fever Control at the Village Level

The outbreak in Zor Zor in 1972 established the presence of Lassa fever in Liberia, something I had predicted two years earlier. Paul Mertens suspected and confirmed more cases subsequently, and the investigations we have conducted the past two years established that Lassa virus infections are common in western Liberia, particularly in Lofa county.

Lassa fever will be controlled in Liberia only by the efforts of Liberians themselves, though outside help will be needed in the initial stages. To this end the proposals I have made for investigations in Liberia have from the beginning required active participation by Liberians. Early efforts in this regard have born fruit, in that physicians and interns graduating from the University of Liberia Medical School are by now aware of the existence of this disease. It has also been gratifying to accept the cooperation of Liberian hospital staffs not only in permitting testing of themselves for evidences of previous Lassa virus infection, but also in assisting in other ways in the surveys we have been conducting.

The next stage of our program involves the determination of incidence of Lassa virus infections in the community. If we are to continue our efforts to make the control of Lassa fever a Liberian enterprise, it will be necessary to raise the consciousness of health workers and the population at the village level to awareness of Lassa fever and what needs to be done about this. This can be done within the provisions of the program which has now been funded; in fact, it will make the program all the more effective. With proper instruction of, and cooperation by, village people and health workers we shall be better able to determine the incidence of Lassa fever in Liberia and to identify potential donors of Lassa fever immune plasma than if the program is conceived only as something being imposed on the community by outside investigators.

To be effective the program will necessarily be related to and under the supervision of the Ministry of Health and Social Welfare and the Division of Preventive Services. Nothing hereinafter suggested should be construed as preempting the functions and responsibilities of the Liberian public health system, but only as a means of implementing them. The following suggestions by the Principal Investigator are subject to revision and modification by appropriate authorities at the national and county level.

### A. General Investigations - Lofa County

If it is possible to incorporate the present health network in Lofa County in the investigation of Lassa fever we shall be able to accomplish

far more than the formal proposal indicates. We shall be able to investigate up to four villages intensively (see below); it is possible that only two of these will be in Lofa County. However, with the help of the present health network we should be able to determine in a rough way the incidence of Lassa fever throughout the County.

In order to accomplish the wider program several steps will be needed.

1. Training of personnel in Health Posts and Health Centers

Information regarding the diagnosis and management of Lassa fever should be incorporated in the continuing education of all health workers at every level. A SOAP outline should be prepared specifically to this end, and personnel alerted to consider Lassa fever in the diagnosis of any fever. Perhaps this has been done already; however, if the following steps are carried out as well whatever instruction that is given will be far more significant.

2. Planning of an "emergency" communication system

There is no question that Lassa fever should be made a reportable disease in Liberia. However, the usual system of reporting illness may not suffice to permit rapid notification of the health authorities and the investigating team.

3. Planning for rapid response

There may be several kinds of response which will be appropriate, in part depending upon the circumstances of the reported illness.

a. Response of the Health Center and/or Hospital

What response and under what circumstances should be thought out, the respective tiers of the health network instructed regarding this, and means for response made available to them, if means such as transportation, plasma, fluids and medication are included in the reponse plan.

One measure that may be appropriate is to designate teams for management of outbreaks. For a time in Nigeria a plan was successfully implemented by which a patient identified as having Lassa fever was surrounded by a "barrier" of nurses, ward attendants and laboratory technicians who were known to have Lassa virus antibodies. It should be possible at this time to designate several teams of such people for Lofa County; we know of about 50 people there who are presumably immune.

b. Response of the Public Health System

Now that means of dealing with Lassa fever are becoming available

in Liberia, Public Health measures may be developed for various contingencies. Should some sort of quarantine be imposed under certain circumstances? This is probably extreme, but is certainly one of the questions which should be addressed.

c. Response of the Investigating Team

If the plans for diagnosis and management of Lassa fever at the village level have been properly developed, it may not be necessary for the investigating team at the LIBR to react on a 24-hour basis, but it should respond soon after a case has been identified to supervise efforts at case finding, arrange to have appropriate tests done and to follow other procedures which will have to be determined. The reactions of the investigative team will be incorporated in their over-all training and instructions, and modified after experience.

4. Development of a record system

It is not enough to identify cases of Lassa virus infection; a system of recording cases, following them up and preparing information regarding occurrence, prevalence, actions taken, treatment given (Lassa fever immune plasma and other modalities) will be required. This will permit the modification of initial plans, the placing of depots of material needed for the management and treatment of cases and outbreaks of Lassa fever, and the accumulation of adequate epidemiologic and clinical information to allow for control of the disease.

B. Special Village Investigations - Lofa County

The proposal which has been funded calls for intensive investigations of Lassa fever in several villages. It has been proposed that two villages in areas of high incidence and two in areas of low incidence be the subjects of investigation. This suggestion should be reviewed at this time.

Villages should be selected with some thought regarding differences among them so that comparisons regarding epidemiology may be made. Thus, it was thought that the two in areas of high incidence might differ in regard to whether or not they were rice-growing. It has been pointed out that villages that did not grow rice might be difficult to discover. An alternate point of differentiation would be whether they grow swamp rice.

The special villages should be communities that will accept the investigative project; it is noted that some are suspicious of any outside workers. Time does not permit extensive survey of villages for their willingness to cooperate; perhaps there are some which by virtue of current relationships to health projects are known to be receptive to efforts to improve their health status. At times the presence of an influential member of the village on a hospital staff, or a person who has received significant health care in a hospital affords quick ingress into a community.

It appears that the community should be large enough to provide at least 500 people as subjects for investigation.

Once such communities have been identified, investigations will continue in them for the duration of the project, at least two years if time permits.

1. Information to village leadership

Those who are important in the village structure, and who will be needed for successful completion of the project will be identified. They will include the village chief and those associated with him in governing of the community, teachers, health workers, pastors, Ministry of Health personnel overseeing the health of the village, traditional healers and others who are informal moulders of public opinion in the village.

The leaders will be informed of the purposes of the survey. Indoctrination will include a description of Lassa fever and its importance to the community, the desirability of determining its incidence as a basis for knowing what measures are needed for its control; an opportunity will be given to obtain their input as to health problems in the community. Then, the procedure which is to be followed will be explained to them. The voluntary aspects of the program will be stressed, as will the importance of obtaining as complete participation as possible from the whole community. Additionally, they will be told of whatever other health measures can be taken in the village in response to their perceived needs.

They will be informed that from time to time, they will be told of the progress of the work. Other steps in information of the village leadership may be included, as the program progresses.

2. Village census

The inhabitants will then be listed by name, family and household, if more than one family lives in the same premises. People will be listed by name, sex, age, relationship within the family and occupation; other data may be added if it seems desirable. A map of the village will be prepared indicating the homes, various buildings such as palaver hut and school which are used in common, other structures, the sources of water, and the location of nearby features such as fields and clumps of trees.

This information will likely be collected over the period of the survey, probably by informal means rather than an initial formal house-to-house canvass of the community; it is vital that the sensitivities of the village be considered.

3. Serological survey

Blood will be obtained from as many of the villagers as possible. They will be asked to hear or read the formal consent statement, and to

sign or affix their mark indicating their consent for the obtaining of blood from themselves or dependent children. Time will be taken to permit adequate translation into their language, and for interpretation of the meaning of the consent form.

The specimen obtained will be handled according to the pertinent protocol.

4. Concurrent investigations

It may be possible to conduct concurrent investigations of the health of the villagers from funds outside the project, and in response to the needs expressed by the village. A separate protocol will be developed for this.

5. Follow up examinations

Villages which are included in the survey will be reinvestigated annually, with testing as at first. Additionally, there will be a program of ongoing surveillance of the village health.

a. By local health workers

All tiers of medical support of the village - health post, health center, hospital - will be requested to record information relating to the health of the villagers. Particular attention will be given to fevers and other severe illness. Any incident of significant illness will be reported promptly to the LIBR through appropriate channels for follow-up serological and other appropriate testing.

b. By the investigative team

The investigative (field) team from the LIBR will make periodic visits to the village to discover from the leadership and village members what illnesses have occurred subsequent to the survey, and will record this information on each person's individual health record. Attempts will be made at this time to keep abreast of immigration and emigration, with proper records to document these changes. Other information relating to the health of the community will be collected at the same time.

In case of an instance of significant illness reported to the LIBR the investigative team will attempt to visit the village as soon as possible, to carry out investigations to determine the cause of the illness, to attempt case finding, to obtain serological specimens from case-contacts in case of fever, and to record all information while it is still fresh in people's minds.

6. Correlations and statistical evaluation

Preliminary tabulation of data will be performed by the field team. More complete evaluation of the data will be made by the Principal

Investigator on a concurrent basis, and later will be refined on the basis of his personal visit to the village and discussions with all tiers of leadership and health personnel. The results of these correlations will be returned to the village in a form which will be understood by them, to assist them in whatever measures are needed to improve the control and management of Lassa fever in their communities.

All information will be made available to the Ministry of Health and Social Welfare, and the final correlations and evaluations will specifically be submitted to the Ministry for its review and whatever action it deems appropriate.

C. Investigations in other counties

Though the primary focus for the investigation will be in Lofa County where our preliminary investigations have indicated its prevalence to be the highest, attempts will be made to conduct small-scale studies in other regions as well. The information collected will likely prove a corrective to some of the conclusions drawn from the Lofa County surveys. Among the investigations contemplated in the project are the following:

1. Village investigations

We have proposed the investigation of two villages in some other region. At present we are considering particular communities near Yekepa, where the prevalence of Lassa fever appears to be one-fourth to one-third of that in Lofa County, but other communities may be selected after consultation with local health authorities. The techniques of the investigation will be similar to those already described for Lofa County.

2. Hospital surveys

It would be useful to conduct surveys among hospital personnel in institutions other than those already investigated. Nothing is known at present of the situation at Cape Mount County, nor in the counties south-east of Nimba and Buchanan. It is possible that there are other pockets of high prevalence for Lassa virus infections in addition to the highly endemic area in Lofa County. Even within the area already surveyed we have found a high prevalence of Lassa virus antibodies among the Phebe hospital staff. It would be important to determine whether this reflects the importation of cases from adjacent Lofa County, with secondary cases among the staff, or significant infection in the Gbarnga area.

3. Other surveys and investigations

If information regarding Lassa fever is generally known, it is possible that reports of illness compatible with the diagnosis may come

from other areas. These should be followed up with appropriate attempts are virological and serological diagnosis, case-finding and epidemiologic investigation.

D. Conclusion

This plan is subject to modification on the basis of experience and special developments that may occur in our knowledge of Lassa fever and its virus. However, it does appear to be a program which is related to Liberian Institutions, one that can form the basis for the on-going control of Lassa fever even after the current specific project has been completed.

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